sequence information in application Serial No. 08/537,765 and the present application are identical.

Therefore, applicants request that the computer readable submission of the Sequence Listing of application Serial No. 08/537,765 be used to fulfill the sequence disclosure requirements for the present application, pursuant to 37 C.F.R.§ 1.821(e). A copy of the paper copy of the Sequence Listing filed in application Serial No. 08/537,765 is enclosed.

Priority/New Matter

Applicants request reconsideration of their claim to priority from U.S. application Serial No. 08/537,765, now U.S. Patent 6,150,169.

Claims 22-29, 32-34, and 41-42 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in a such a way as to reasonably convey to one skilled in the art that the applicants were in possession of the invention at the time the application was filed. Applicants traverse.

This application is a divisional of Serial No 08/537765, which was itself derived from International Application PCT/GB94/00849. All of the pending claims are supported by the original disclosure of International Application PCT/GB94/00849, thich is identical to the present application.

Basis for formula without X and Y and without a promoter

At page 6 the formula 5' X-A-P-B-Q-C-Y 3' is given for a construct according to one aspect of the invention, in which:

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X and Y	are, separately, DNA sequences substantially homologous with a host gene locus,
P	is an internal ribosome entry site (IRES),
Q	is a heterologous gene sequence, and
A, B and C	are optional linker sequences.

In the first complete paragraph at page 14, it is specified that the invention includes using a promoterless construct according to the invention and allowing the construct [1] to integrate randomly within a host genome. In the first complete paragraph at page 11 it is explained that random integration does not require homologous recombination with a target gene. (Reference can also be made to the first paragraph of page 1, where the invention is discussed in connection with "inserting heterologous gene sequences into a host genome" without limiting to homologous recombination.) It is therefore absolutely clear that to a skilled person that in the embodiment of the invention that covers random integration, homologous sequences X and Y of the above formula embodiment are not needed and also that a promoter is not used.

Basis for polyadenylation signal

Original claim 7 makes it clear that a polyadenylation signal at the 3'(downstream) end of the heterologous gene sequence can be included and was contemplated as one aspect of the invention. Reference can also be made to the

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[1] "construct" rather than "vector" has now been used in the method claims for consistency with the "construct" claims.

paragraph bridging pages 10 and 11, where it is indicated that it is preferred that there is a polyadenylation signal at the 3'(downstream) end of the heterologous gene.

Basis for splice acceptor site

Original claim 8 makes it clear that a splice acceptor site located 5'(upstream) of the heterologous gene sequence can also be included and was contemplated as one aspect of the invention.

Thus, the combination of features identified by the Examiner as unsupported by the specification is, in fact, fairly based upon the disclosure of PCT/GB94/00849, U.S. Serial No. 08/537,765, and the present application and does not introduce any new matter.

Enablement

Claims 22-29, 32-34, and 41-42 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Applicants traverse.

As indicated above, the claimed constructs and methods are fully supported by the application as filed and the priority applications. A skilled person would be able to make these constructs using standard genetic engineering techniques. For example, linker sites could be used to join together individual elements (see e.g. the last complete paragraph of page 7). The individual elements of the constructs are all well known and a skilled person would be in a position to provide these.

It is also important to appreciate that the use of gene trap constructs was well known before the priority date of the present invention. Reference can be made for

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example to Skarnes W.C., Biotechnology, 8, 827 et seq. (1990) and to Skarnes et al., Genes & Development, 6, 903-18 (1992) (copies enclosed). The latter document is cited in the paragraph bridging pages 4 and 5 of the present application in the context of constructs allowing random integration into host genes.

The constructs of the present invention do not have to be used in any unusual manner but can utilize standard techniques, such as transfection and screening for expression of heterologous proteins.

With respect to the claimed cells, it is important to appreciate that they have been limited to mouse embryonic stem cells or to descendants thereof. (This should not be construed as an admission that the invention is only suitable in respect of such cells. For the record, the invention is believed to be suitable for use in a wide variety of cells and the application is believed to provide an enabling disclosure in respect of a wide variety of cells.) The Examiner has acknowledged that ES technology has been applied to the mouse system and that embryonic stem cells have successfully demonstrated germ-line transmission in the mouse system. The claim to a mouse comprising the aforesaid descendant cells is therefore enabled.

The Examiner has referred to the unpredictability of random integration. However the claimed invention is particularly useful precisely because it can be used to easily identify and/or select for random integrations that result in expression of heterologous sequences, without the need for advance knowledge of a host cell's genome or of a host cell's expression pattern. If random integration does not insert the heterologous sequence within genes or within active genes of a host cell, the resultant host cells do not express the relevant heterologous sequence and are simply not

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selected or identified. If integration does occur within an expressed host gene the heterologous sequence can then be expressed in the host cell and can be identified/selected by virtue of its expression product(s). For example the heterologous sequence may include a region encoding an antibiotic resistance marker, whereby expression of the marker allows selection using antibiotic-containing media.

In summary, although integration is random, a skilled person would readily be able to identify/select for the integration of heterologous genes that are expressed in a host cells genome by virtue of their expression products. This would not involve unreasonable experimentation because the skilled person would naturally use large numbers of cells rather than experimenting upon a single cell at a time. Those skilled in the art of genetic engineering are of course well used to using large numbers of cells for to identifying/selecting events that may occur at low frequency. Indeed, cells in culture are generally used in large numbers.

The Examiner's comments regarding the examples have been noted. However, the examples do demonstrate that a construct comprising an IRES, a splice acceptor site and a heterologous gene sequence without a promoter can be integrated into a host cell genome and can be used to obtain successful expression in the host. It was already well known that integration could occur by events involving random/non-homologous recombination as discussed at pages 4 and 5 of the present application. Thus, the examples do provide support for the claimed invention and do not in any way support a conclusion of non-enablement. In any event, specific examples are not essential here because the skilled person would readily be able to perform the invention

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without them in the light of the details provided in the application and in the light of knowledge in the art at the time (as discussed above).

The Examiner has suggested removing the use limitation from claim 32. This has been done because claim 32 is to a construct *per se* and therefore a use feature is not required. (This should not be construed as an admission that the construct is not suitable for said use. For the record, the construct is believed to be suitable for this use and the application is believed to provide an enabling disclosure in respect of this use.)

Given that claim 32 is a product claim and does not now specify a use in respect of mouse cells, the limitation to mouse cells has also been removed from claim 34 for consistency.

Anticipation

Claims 22-24, 28-29, and 32-33 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,248,934, which claims priority from U.S. provisional application filed on October 26, 1998. Applicants submit that this document is not prior art to the pending claims.

The pending claims are fully supported by International Application PCT/GB94/00849 and, as such, are entitled to an effective filing date of no later than 21 April 1994 - i.e. at least 4 years before any possible §102(e) date of U.S. Patent 6,248,934. Thus US patent 6,248,934 is not prior art and cannot anticipate the claimed invention.

Conclusion

Applicants believe that the claims are now in condition for allowance and request early notification of the same.

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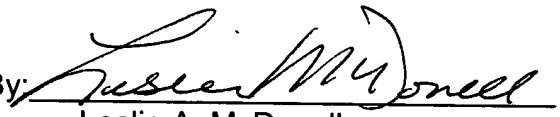
Applicants believe that any extension of time required to file this Amendment and Response is accounted for by the accompanying Petition for Extension of Time under 37 C.F.R. 1.136(a). However, if Applicants are in error, please grant any extensions of time required and charge any additional required fees to deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: December 5, 2002

By: 

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Services under 37 C.F.R. § 1.8 on December 5, 2002 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

BY: Rachel Venturi

APPENDIX TO AMENDMENT FILED DEMBER 5, 2002

Claims Marked to Show Changes Made

22. (Three Times Amended) A method of inserting a heterologous gene coding sequence into an endogenous gene in a mouse embryonic stem cell genome and expressing said heterologous gene coding sequence, comprising the step of transforming the mouse embryonic stem cell with a [random gene trap vector comprising a] DNA construct, wherein the DNA construct [(k)] lacks a promoter, and [(ii)] comprises the sequence:

5' A-P-B-Q-C 3'

in which

P is an internal ribosome entry site (IRES),

Q is the heterologous gene sequence, and

A, B and C are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q

[5' X-A-P-B-Q-C-Y 3'

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in which

X	comprises a splice acceptor sequence;
Y	comprises a polyadenylation signal;
P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene sequence, including a translation start codon; and
A, B and C	are, separately, optional linker sequences].

23. A method according to Claim 22 where the heterologous gene coding sequence is randomly inserted into an endogenous gene so that transcription of the heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

24. A method according to Claim 22 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

26. A method according to Claim 22 further comprising the step of identifying cells expressing the heterologous gene coding sequence.

27. A method according to Claim 26 wherein the heterologous gene coding sequence also codes for a selectable marker and the method comprises selecting cells that express the selectable marker.

28. A mouse embryonic stem cell comprising a heterologous gene coding sequence inserted by the method of Claim 22.

29. (Twice Amended) A descendant of the mouse embryonic stem cell according to Claim 28, wherein the descendant has inherited the inserted heterologous gene coding sequence.

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30. (Amended) A mouse [An animal] comprising a cell according to Claim 29 [heterologous gene coding sequence inserted by the method of Claim 22].

31. (Amended) A descendant of a mouse [an animal] according to Claim 30, wherein the descendant has inherited the inserted heterologous gene coding sequence.

32. (Three Times Amended) A DNA construct [for randomly inserting a heterologous gene sequence into a mouse cell genome, said construct lacking a promoter and] comprising the sequence:

5' A-P-B-Q-C 3'

in which

P	is an internal ribosome entry site (IRES),
Q	is a [the] heterologous gene sequence, and
A, B and C	are, separately, optional linker sequences;

wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of Q

[5' X-A-P-B-Q-C-Y 3'

in which

X	comprises a spice acceptor sequence;
Y	comprises a polyadenylation signal;
P	is an internal ribosome entry site (IRES);
Q	is the heterologous gene sequence, including a translational start codon; and
A, B and C	are, separately, optional linker sequences].

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33. A DNA construct according to Claim 32 in which the splice acceptor permits functional integration of the heterologous gene into an intron sequence.

34. (Twice Amended) A DNA construct according to Claim 32 in which the heterologous gene sequence additionally codes for a selectable marker to facilitate selection of [mouse] cells containing a heterologous gene that has been inserted into an endogenous gene.

41. A method according to Claim 22 wherein the heterologous gene coding sequence also codes for antibiotic resistance, and the method comprises selecting cells that express the antibiotic resistance.

42. A DNA construct according to Claim 32 wherein the heterologous gene sequence additionally codes for antibiotic resistance.

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